Remarks

Rejection Under 35 U.S.C. § 112, first paragraph, written description

Claim 1 was rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection.

Analysis

During the discussion at the interview in regard to this rejection, the Examiners raised the issue of the relevance of Ex parte Grasselli, 231 USPQ 393 (Bd. App. 1983) aff'd mem 738 F.2d 453 (Fed. Cir. 1984). Ex parte Grasselli was decided by a three member panel of the then-Board of Appeals. As such, the decision carries no precedential value and constitutes only the law of that case. The Federal Circuit affirmed the decision of the Board in an "unpublished" opinion that by definition is not precedential. The legal standards by which the written description issue raised in the rejection should be evaluated are set forth at pages 13-14 of the Response. Thus, Ex parte Grasselli, is not relevant in considering the written description rejection.

Withdrawal of the rejection for the reasons set forth in the Response is again courteously solicited.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-17 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection.

Analysis

During the discussion at the interview in regard to this rejection, the arguments set forth in the Response were reviewed. For those reasons it is believed that the metes and bounds of the claims can be readily ascertained by a person of skill in this art.

Withdrawal of the rejection for the reasons set forth in the Response is again courteously solicited.

Rejections Under 35 U.S.C. § 102 and § 103

Claims 1-3, 7-10 and 13-17 were rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent Application Publication No. 2003/0232086 to McCadden ("McCadden). Claims 1-3, 7-10, 13 and 17 were rejected under 35 U.S.C. § 102(b) as disclosed by U. S. Patent No. 5,219,877 to Shah *et al.* ("Shah"). Claims 1-3, 7-13 and 17 were rejected under 35 U.S.C. § 102(b) as disclosed by U. S. Patent No. 6,075,056 to Quigley *et al.* ("Quigley").

Claims 4-6, 11 and 12 were rejected under 35 U.S.C. § 103(a) as unpatentable over McCadden. Claims 4-6 were rejected under 35 U.S.C. § 103(a) as unpatentable over Shah. Claims 11 and 12 were rejected under 35 U.S.C. § 103(a) as unpatentable over Quigley. Claims 14-16 were rejected under 35 U.S.C. § 103(a) as unpatentable over Shah in view of U.S. Patent No. 5,686,089 to Mitra ("Mitra"). Claims 14-16 were rejected under 35 U.S.C. § 103(a) as unpatentable over as unpatentable over Shah in view of U.S. Patent No. 6,444,647 to Robinson ("Robinson").

Analysis

1. Rejections based upon McCadden

The Examiners stated at the interview that rejections based upon McCadden would be withdrawn in view of the declaration filed under 37 CFR § 1.131 that accompanied the Response. The Examiners are thanked for this action.

2. Anticipation rejection based upon Shah

The following disclosure of Shah was discussed at the interview:

A preferred gel formulation of the present invention containing sulconazole nitrate 1% w/w in combination with hydrocortisone-17-valerate 0.2% w/w has the following composition:

Component	Amount, % w/w
sulconazole nitrate	1.0
hydrocortisone-17-valerate	0.2
lauryl alcohol	10.0
ethyl alcohol	50.0
1,2,6-hexanetriol	26.5
isopropyl myristate	7.5
PPG-20 methyl glucose ether	3.0
hydroxypropylcellulose	0.9
salicylic acid	0.5
BHA	0.2
BHT	0.2

The Response stated:

While not relied upon by the examiner it is noted that a preferred gel formulation containing 0.2% w/w hydrocortisone-17-valerate is set forth at column 5, lines 30-45 of

Shah, as well as in Examples 1, 6 and 7. However, the Chart lists "Westcort Ointment, 0.2%" as containing hydrocortisone valerate and as a Class 4—Mid-Strength composition. The Chart also lists "Westcort cream, 0.2%" as containing hydrocortisone valerate, but as a Class 5—Lower Mid-Strength composition. According to McCadden, the potency of a steroid gel composition is in between an ointment and a cream. Thus, the exemplified gel formulations of Shah are outside the scope of claim 1 since claim 1 only includes low to low-medium potency steroids.

The Examiners asked at the interview why it was reasonable to assume that the illustrated gel formulation is outside the scope of claim 1 since, according to McCadden, gel forms of topical anti-inflammatory steroids have a potency between ointments and creams. In other words, why isn't it equally reasonable to assume that the gel formulation of Shah is a low-medium potency formulation?

The best answer to this question is found in Shah itself as the compositions of Shah are self-styled as "mid-potency." See, e.g., column 4, lines 3-16. Thus, the formulations described in Shah such as the compositions set forth above is formulated by Shah as a mid-potency formulation. In this regard, the Examiner should note that the formulations of Shah are prepared to possess "superior skin penetration properties." Id., column 3, lines 4-7. Enhanced skin penetration leads to enhanced potency. Claim 1 requires the presence of low to low-medium potency steroids, not the mid-potency formulations described by Shah. Thus, when Shah is read

in its entirety and in the proper context, it is seen that the formulations according to Shah are mid-potency and outside the scope of the claims.

Withdrawal of this rejection is again courteously solicited.

3. Anticipation rejection based upon Quigley

The arguments set forth in the Response based upon In re Arkley, 455 F.2d 586, 587, 172 USPQ 524, 526 (CCPA 1972) were discussed. Withdrawal of this argument based upon the arguments is again courteously solicited.

4. Obviousness rejections

The declaration filed under 37 CFR § 1.132 by co-inventor Dr. Jay Goldstein (Goldstein Declaration) was discussed at the interview. The Examiners raised two concerns in regard to the Goldstein Declaration, (1) whether a proper comparison has been made and (2) whether the showing was commensurate in scope with the claims.

Dr. Goldstein has explained that it would be unethical to compare the formulations used in the present claims to stronger, more potent steroids due to the risk of major untoward side effects. Goldstein Declaration, paragraph 3. The Examiners asked at the interview whether there are in vitro tests that can be used. When the prior art and the nature of the discovery of the present inventors are viewed together, it is seen that further testing, whether in vivo or in vitro is not needed.

The use of high potency anti-inflammatory steroids in combination with antifungal agents was known in the art at the time of present discovery. See, specification, pages 1-2. The high potency steroids used in these prior art formulations were known to cause serious side effects.

Id. Reference in this regard is made to Hengge (Hengge, et al., *J. Am. Acad. Dermatol*, 54:1-15 (2006)). Hengge reviews the adverse side effects of topical glucocorticosteroids. One of the side effects is that when anti-inflammatory steroids are used to suppress inflammation, fungal and bacteria growth flourishes. Id., paragraph bridging the columns, page 8. In discussing so-called combination products, Hengge indicates that, while pediatricians frequently prescribed fixed combinations of betamethasone and clotrimazole, the study indicated the importance of monotherapy. Id., right hand column, page 12. Thus, it was counterintuitive to use a combination low to low medium potency anti-inflammatory steroids and antifungal agents as one would have to go against the preference for monotherapy as well as being concerned that using anti-inflammatory steroids in treating a fungal infection would allow the fungus to flourish.

The present discovery is that low to low-medium potency anti-inflammatory steroids can be used in combination with antifungal agents in a safe and effective manner. There is no question that products based upon high potency anti-inflammatory steroids and antifungal agents were useful in topically treating dermatological conditions. However, the use of such products was and is limited by the serious side effects caused by the high potency anti-inflammatory steroids. It was unexpected that dermatological conditions could be treated in a safe and effective manner by using compositions based upon low to low-medium potency anti-inflammatory steroids and antifungal agents. Thus, there is no need for any further testing. The applied prior art teaches away from using the claimed compositions as this prior art teaches one should use formulations that contain anti-inflammatory steroids having a potency higher than that set forth in claim 1. It is the discovery by applicants that dermatological conditions that

were previously treated by a combination of high potency anti-inflammatory steroids and antifungal agents can now be treated by low to low-medium anti-inflammatory steroids in combination with antifungal agents with the attendant reduction in side effects that is not taught by the prior art.

That the claimed combinations of low to low medium potency anti-inflammatory steroids and antifungal agents are counterintuitive and nonobvious is also seen from a consideration of three documents cited in Hengge; Fleischer (Fleischer, et al., *Clin. Ther.*, 21:1725-31 (1999)), Shaffer (Shaffer, et al., *Fam. Med.*, 32:561-5 (2000)), and Stern (Stern, *J. Am. Acad. Dermatol.*, 35:183-6 (1996)), as well as a document cited in Fleischer, Smith (Smith, et al., *J. Am. Acad. Dermatol.*, 39:43-47 (1998)).

Fleischer analyzed data in regard to prescription of high-potency corticosteroid agents (monotherapy) and clotrimazole-betamethasone dipropionate (combined therapy) by pediatricians. Fleischer reiterates that betamethasone dipropionate is an ultrahigh or high potency steroid and its use can result in significant side effects. Id., page 1729, left hand paragraph. Fleischer also states:

> When a superficial fungal infection can be diagnosed, more effective, less costly topical antifungal medications are available, including prescription drugs such as econazole or over-the-counter agents such as miconazole. In 2 studies, single antifungal agents exhibited greater antifungal efficacy than did 2 combination products (clotrimazole-betamethasone dipropionate and clotrimazole/1 % hydrocortisone), and

> they cost less. In 1 study, the mycologic cure rate for tinea cruris or tinea corporis with clotrimazole-betamethasone dipropionate was 65%. In contrast, monotherapy with antifungal agents such as topical naftifine, econazole, and terbinafine provided cure rates of 80% to 83% for tinea corporis and tinea cruris, respectively.

Id., page 1729, right hand column

As set forth on pages 1-2 of the specification the combination products used in the referenced studies contain a very potent anti-inflammatory steroid, betamethasone dipropionate, or one that lacks significant anti-inflammatory properties, 1% hydrocortisone. This is a clear teaching away from the combinations of low to low-medium potency anti-inflammatory steroids and an antifungal agent set forth in the present claims.

Fleischer also discusses the potential use of a low-potency topical corticosteroid such as hydrocortisone plus a single-agent antifungal product, stating that such a combination is "likely to be more effective, less expensive, and less risky than use of a combination topical antifungal-topical corticosteroid agent," citing Smith. Id., page 1729 paragraph bridging the columns. A review of Smith shows that it does not support the speculative statement of Fleisher.

Smith reviewed data in regard to prescription of clotrimazole-betamethasone dipropionate (combined therapy) and states that combination therapy is less effective as antifungal agents but do provide antiinflammatory activity. Id., page 43, paragraph bridging columns. Importantly, Smith states "[i]t is known that for fungal skin infections, combination

corticosteroid/antifungal preparations are less effective than monotherapy and may even exacerbate the disease" and that "nondermatologists may be unaware of the greater side effects and lower antifungal efficacy of combination agents." Id. paragraph bridging columns. There is no disclosure in Smith of a low-potency topical corticosteroid such as hydrocortisone plus a single-agent antifungal product as suggested by Fleischer. Thus, the statement of Fleischer in this regard is speculative and not fact-based. Reading Fleischer and Smith together, it is seen that combination therapy included use of betamethasone dipropionate, a very potent anti-inflammatory steroid, and that such combination therapy was disfavored in favor of monotherapy using a single antifungal agent. Again, these documents teach away for the compositions called for by the present claims.

Shaffer was published in 2000 and in view of the Examiner's acceptance of the declaration filed under 37 CFR § 1.131, Shaffer is not available as prior art. However, it should be considered by the Examiner as it contains relevant information. For example, Shaffer states:

> When is it appropriate for clinicians to prescribe clotrimazole/betamethasone diproprionate? When the diagnosis of a fungal infection is certain, antifungal monotherapy agents are more effective and less expensive. Similarly, if the diagnosis of an inflammatory process is certain, topical corticosteroid monotherapy of the appropriate potency is also effective and less expensive. It is intriguing to speculate as to what accounts for the frequent use of clotrimazole/betamethasone diproprionate in young children and for sensitive sites. It appears not to be related to lack of knowledge

concerning the potency of the drug. While most pediatricians who prescribe clotrimazole/betamethasone diproprionate do not know that it is a high-potency topical corticosteroid, knowing the potency does not appear to influence prescribing patterns Railan D, Feldman SR, Fleischer AB Jr, unpublished data, 2000).

Id., page 564, right hand column.

Shaffer also states:

Use of clotrimazole/betamethasone diproprionate may represent the response to uncertainty in clinically differentiating between fungal and inflammatory disorders, a problem for nondermatologists,16,17 or the impression that both fungal and inflammatory processes are contributing to the etiology of the condition, such as a combination of irritant dermatitis and fungal infection in warm, moist occluded areas. A pragmatic approach to this conundrum is to prescribe combination treatment, but the high-potency topical corticosteroid in clotrimazole/betamethasone diproprionate is not appropriate for this use. Other agents with both antiirritant and antifungal properties may represent a practical approach to treating patients in such situations and would be an improvement over currently available combination treatments. When combination treatment is required, clinicians should consider combining hydrocortisone or other low-

potency corticosteroid agents (desonide or aclometasone) and monoagent antifungal therapy to provide for safer and more efficacious treatment.

Id. Shaffer is not available as prior art to the pending claims. Even if it was, the suggestion in the document in regard to combination therapy using desonide or aclomethasone and a monoagent antifungal product is just that, a suggestion. Reading Fleischer, Smith and Shaffer together, it is clear that at the time of the present discovery, treatment of dermatological conditions was unpredictable. These documents establish that at the relevant time, persons of skill in this art prescribed combination products containing a high potency anti-inflammatory steroid or prescribed monotherapy. It remained for the present inventors to go against the conventional wisdom in the art and use the claimed combination therapy and discover that the claimed combinations can be used to effectively treat dermatological conditions with a reduced risk of side effects.

Stern is consistent with the disclosures of Fleischer, Shaffer and Smith. In discussing combination therapy, Stern describes the use of a "medium- or high potency topical corticosteroid as a combination product (i.e., with a topical antiinfective agent)." Stern does not provide any detail as to the antiinfective agent discussed but specifically limits the combination therapy to medium- or high potency corticosteroids. This disclosure constitutes yet another teaching away from the subject matter of the present claims.

Stern also provides evidence of the unpredictability of this art area, stating "guidelines for optimizing therapy and for rational prescribing with respect to the choice of a specific agent or

even the selection of which potency of topical corticosteroid is best for the individual patient are not well established." Id., page 186, paragraph bridging columns. Again, it remained for the present inventors to go against the conventional wisdom in this unpredictable art and discover that the compositions set forth in the present claims do in fact effectively treat dermatological conditions with a reduced risk of side effects.

In regard to the Examiner's concern in regard to the scope of the showing in the Goldstein Declaration, it is noted that:

> ... appellant is not required to test each and every species within the scope of the appealed claims and compare same with the closest prior art species. Rather patentability is established by a showing of unexpected superiority for representative compounds within the scope of the appealed claims. What is representative is a factual question which is decided on a case-by-case basis.

Ex parte Winters, 11 USPQ2d 1387, 1388 (Bd Pat App Int 1989).

The Federal Circuit has stated in the context of considering showings of unexpected results that there is a "presumption of similar properties for similar compositions." In re Soni, 54 F.3d 746, 751, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995). This presumption should hold here. The Goldstein Declaration provides ample evidence that the claimed compositions effectively

and safely treat various dermatological conditions. Fleischer, Shaffer, Smith and Stern establish that this field is unpredictable and that the direction the present inventors took in developing this technology was counterintuitive. Simply put, there is no basis in the applied art to have expected that "less is more" as is demonstrated in the Goldstein Declaration. Now that the present inventors have demonstrated the claimed combinations do work as indicated, persons of skill in the art would readily expect that compositions similar to those used in Goldstein Declaration that are included within the claims will also work in this manner. Thus, the results set forth in the Goldstein Declaration are unexpected and commensurate in scope with the claims.

When the evidence of nonobviousness now of record including the Goldstein Declaration, Fleischer, Smith, Shaffer and Stern is weighed against the evidence of obviousness, the clear weight of the body of evidence favors a finding of nonobviousness.

Withdrawal of all obviousness rejections is again courteously solicited.

Summary

The Examiners are thanked for considering this supplemental response. When the arguments made herein are considered with the arguments made in the Response, it is believed that all rejections have been overcome. If there is any further issue that the Examiners believe needs to be discussed they are asked to telephone the undersigned.

Allowance of claims 1-17 is respectfully solicited.

Respectfully submitted,

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